shown for intestinal slices [28] and much higher than those reported for 2D systems [8, 26]. These data suggest suitability of this model for drug induced metabolic and transporter studies that cannot be achieved by previous adult, fetal, or Caco-2 monolayers [8, 26]. The dual presence of transporters and enzymes in the 3D bioprinted intestinal tissue model suggests that it could be used to shed light on complex interactions, such as those seen with overlapping P-gp/CYP3A4 substrates [29].

[0336] Gastrointestinal toxicity is a common clinical adverse event in drug development often associated with a high prevalence of diarrhea, an outcome that cannot be accurately predicted or characterized with current in vitro models or in vivo models [4, 5, 30]. NSAID indomethacin was used to successfully validate a toxicity response of the 3D bioprinted intestinal tissue. Tissues responded in a dose-dependent manner with decreased TEER and increased cell disruption, correlating with a decrease in barrier function similar to that reported in in vitro [31] and in vivo outcomes [4]. The 3D bioprinted intestinal tissue also responded to the toxic inflammatory stimulus TNFα, a clinical target [30], with decreased barrier function and upregulation of inflammatory genes, consistent with previous 2D models [32]. These data suggest that the 3D bioprinted intestinal model may be applied to screen other known classes of compounds, such as chemotherapeutics [5], that have off target toxicity in the intestine and combined with long term viability, indicates that the model is amenable to dosing and recovery studies. Furthermore, upregulation of inflammation markers suggests that future applications could include modeling chronic disease such as inflammatory bowel disease (IBD), Crohn's disease, and colitis [4, 5, 30]. Additional complexity can be achieved by incorporating immune cells and/or using intestinal cells isolated by diseased donors [13, 24].

[0337] In summary, disclosed is a novel in vitro 3D bioprinted intestinal tissue model with increased complexity and function compared to standard models. The fully human 3D bioprinted intestinal model recapitulates the intestinal mucosa, with physiological barrier function and expression of key functional transporters and metabolic enzymes. The 3D bioprinted intestinal tissue provides a flexible platform compatible with assays for barrier function, permeability, metabolism, transport, and toxicity.

[0338] Additional applications of the 3D bioprinted intestinal tissue model include utilization as a disease model to characterize therapeutic targets for multiple applications including inflammation, infectious disease, and endocrine biology. High expression of enzymes involved in fatty acid metabolism in the 3D bioprinted intestinal tissue indicate a potential application for evaluating compounds targeting these enzymes to combat obesity [33]. Furthermore, the interstitium of the 3D bioprinted intestinal model provides a platform for characterizing fibrogenesis, including injury and regeneration such as wound healing, a disease phenotype that cannot be adequately modeled in 2D. To better mimic the native microenvironment, additional applications can utilize cells from different segments of the GI tract for comparison to the ileum such as the duodenum, colon and rectum and could integrate laminar flow. The 3D bioprinted intestinal model could be specialized by addition of a variety of cellular inputs to add complexity by incorporating, for example, endothelial cells to model vasculature, smooth muscle cells to more accurately model the submucosa and gastrointestinal motility, and immune cells to model disease states. Cancer cells can also be added to model tumor behavior in a 3D environment. Because of the native tissue-like multicellularity and architecture, bioprinted 3D intestinal tissues provide a unique opportunity to study complex multifaceted processes including secretion, transport, cell-cell interactions and pathogenic processes across multiple applications in a controlled system.

[0339] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[0340] All patents, patent applications and publications cited herein are fully incorporated by reference herein.

REFERENCES

[0341] 1. Alqahtani, S., L. A. Mohamed, and A. Kaddoumi, Experimental models for predicting drug absorption and metabolism. Expert Opin Drug Metab Toxicol, 2013. 9(10): p. 1241-54.

[0342] 2. Peters, S. A., et al., Predicting Drug Extraction in the Human Gut Wall: Assessing Contributions from Drug Metabolizing Enzymes and Transporter Proteins using Preclinical Models. Clin Pharmacokinet, 2016. 55: p. 673-96.

[0343] 3. Jones, C. R., et al., Gut Wall Metabolism. Application of Pre-Clinical Models for the Prediction of Human Drug Absorption and First-Pass Elimination. Aaps j, 2016. 18(3): p. 589-604.

[0344] 4. Boelsterli, U. A., M. R. Redinbo, and K. S. Saitta, Multiple NSAID-Induced Hits Injure the Small Intestine: Underlying Mechanisms and Novel Strategies. Toxicol Sci, 2013. 131(2): p. 654-67.

[0345] 5. Aprile, G., et al., Treatment-related gastrointestinal toxicities and advanced colorectal or pancreatic cancer: A critical update. World J Gastroenterol, 2015. 21(41): p. 11793-803.

[0346] 6. Bentz, J., et al., Variability in P-Glycoprotein Inhibitory Potency (IC(50)) Using Various in Vitro Experimental Systems: Implications for Universal Digoxin Drug-Drug Interaction Risk Assessment Decision Criteria. Drug Metab Dispos, 2013. 41(7): p. 1347-66.

[0347] 7. Prueksaritanont, T., et al., Comparative studies of drug-metabolizing enzymes in dog, monkey, and human small intestines, and in Caco-2 cells. Drug Metab Dispos, 1996. 24(6): p. 634-42.

[0348] 8. Yamaura, Y., et al., Functional Comparison of Human Colonic Carcinoma Cell Lines and Primary Small Intestinal Epithelial Cells for Investigations of Intestinal Drug Permeability and First-Pass Metabolism. Drug Metab Dispos, 2016. 44(3): p. 329-35.

[0349] 9. Sato, T., et al., Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium. Gastroenterology, 2011. 141(5): p. 1762-72.

[0350] 10. Yin, X., et al., Niche-independent high-purity cultures of Lgr5+ intestinal stem cells and their progeny. Nat Methods, 2014. 11(1): p. 106-12.